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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/380,704	06/06/2000	ASHLEY I. BUSH	0609.4350001	2953

7590 05/22/2003

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/380,704	BUSH ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,37,38 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *53* is/are allowed.

6)☒ Claim(s) *1,2 and 37* is/are rejected.

7)☒ Claim(s) *38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of Application, Amendments and/or Claims

The amendment of 26 February 2003 (Paper No. 23) has been entered in full. Claims 1-2, 37-38, and 53 are amended.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-2, 37-38, and 53 are under consideration in the instant application.

Sequence Compliance

The Applicant's response to the Notice to Comply with Sequence Listing Requirements under 37 CFR §1.821 (Paper No. 23, 26 February 2003) has been considered and is found persuasive. Therefore, the requirements set forth in the Notice to Comply (Paper No. 21, 26 August 2002) are withdrawn.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pg 3 of the previous Office Action (Paper No. 21,26 August 2002) are *withdrawn* in view of the amended specification (Paper No. 23, 26 February 2003).

2. The objection to claims 1-2, 37-38, and 53 at pg 3-4 of the previous Office Action (Paper No. 21, 26 February 2003) is *withdrawn* in view of the amended claims (Paper No. 23, 26 February 2003).

3. The rejections to claims 1-2, 37-38, and 53 under 35 U.S.C. § 112, second paragraph, as set forth at pg 6-7 of the previous Office Action (Paper No. 21, 26 August 2002) are *withdrawn in part* in view of the amended claims (Paper No. 23, 26 February 2003). Please see section on 35 U.S.C. § 112, second paragraph, below.

4. The rejections to claims 1-2, 37-38, and 53 under 35 U.S.C. § 112, second paragraph as set forth at pg 6-7 of the previous Office Action (Paper No. 21, 26 August 2002) are *withdrawn* in view of the amended claims and Applicant's persuasive arguments (Paper No. 23, 26 February 2003). Please see section on 35 U.S.C. 112, second paragraph, below.

Information Disclosure Statement

5. It is noted to Applicant that the references cited in the IDSs of February 15, 2001 and January 16, 2001 have been considered and signed by the Examiner in the previous Office Action. The patents and search reports listed in the IDSs of November 30, 2000 and December 27, 2000 have been considered. The publications listed on the IDSs of August 14, 2000 and November 30, 2000 have been located and considered by the Examiner. However, a clean PTO-1449 must be resubmitted so the publications can be initialed. The publications listed on the IDSs of December 27 2000, January 18, 2000, and March 14, 2000 have not been considered by the Examiner because the publications are not present in the application. The Examiner acknowledges the copies of the PTO return postcards submitted by the Applicant as evidence that the PTO received all the references on the dates above. However, the Examiner cannot consider the references unless copies of the publications are present in the case. It is noted that the IDS form for March 14, 2000 is not present in the application. It appears that due to the large number of references, the publications and missing IDS form have become separated from the application. The Examiner will consider the references if resubmitted and suggests that Applicant have the publications and clean PTO-1449 forms hand carried to Crystal Mall 1; 7th floor, 1911 South Clark Place; Arlington, VA 22202. No fees will be incurred. If Applicant opts for this suggestion, please notify the Examiner so she can personally pick them up.

Claim Objections

6. Claim 38 is objected to because of the following informalities:

7. Claim 38 is objected to as being dependent upon a rejected base claim.

Appropriate correction is required.

35 USC § 112, first paragraph

8. Claims 1-2 and 37-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth at pg 4-6 of the previous Office Action (Paper No. 21, 26 August 2002).

The claims are directed to a method of treating amyloidosis in a subject comprising administering to said subject an effective amount of (a) bathocuproine or a hydrophobic derivative thereof; and (b) one or more pharmaceutically acceptable carriers or diluents; for a time and under conditions to bring about said treatment; and wherein said chelator reduces, inhibits or otherwise interferes with amyloid beta peptide (Aβ)-mediated production of radical oxygen species. The claims also recite further administering to the subject as effective amount of indomethacin. The claims are directed to a pharmaceutical composition comprising (a) bathocuproine or a hydrophobic derivative thereof; and (b) one or more pharmaceutically acceptable carriers or diluents. This composition further comprises a compound, indomethacin.

Applicant's arguments (Paper No. 23, 26 February 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that absence of a working example is not sufficient to establish a *prima facie* case of non-enablement and cites *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987). Applicant argues that the specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would have been able to practice it without undue experimentation and cites *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). Applicant also contends that the specification, supplemented with the knowledge possessed by those of skill in the art, would have provided sufficient guidance for practicing and/or making and using the subject matter encompassed by the present claims. Applicant concludes that the absence of a working example in the specification does not support the rejection for a lack of enablement.

Applicant's arguments have been fully considered but are not found to be persuasive. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed". The specification of the instant application outlines a prophetic procedure for a method of treating amyloidosis in a subject by administration of bathocuprione and a pharmaceutically acceptable carrier (pg 43-44). However, this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The claimed method may not necessarily treat amyloidosis *in vivo*. The skilled artisan must resort to trial and error experimentation to determine the optimal quantity of bathocuprione/indomethacin to be administered, as well the duration of treatment and route of administration. Such trial and error experimentation is considered undue. There is little guidance in the specification at pg 45-49 regarding specific dosages, duration of treatment, and type of

administration for bathocuprione. Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily treat amyloidosis by administration of bathocuprione and indomethacin to a subject. Additionally, the Examiner's indication of the absence of a working example is only one facet of the Wands factors, which were provided in the previous Office Action (Paper No. 21, 26 August 2002).

(ii) Applicant asserts that in the Examiner's Office Action, there has been no evidence or explanation set forth to explain why the *in vitro* results presented in the specification are not indicative of *in vivo* results. Applicant submits that there has been no evidence presented to suggest that the ability of bathocuprione to promote the solubilization of Aβ *in vitro* would not reflect the ability of bathocuprione to promote the solubilization of Aβ when administered to a subject suffering from amyloidosis. Applicant argues that the existing evidence in the art strongly support the correlation between the *in vitro* results presented in the specification and the results that would be obtained in a subject. Applicant asserts that the physiological conditions that exist in brain homogenates (e.g., pH, ion concentration, macromolecular content, etc.) closely approximate the conditions found in the brain tissue environment *in vivo*. Applicant also

asserts that it was known in the art that the regulation of zinc and copper in the brain is abnormal in AD and that these metals are integral components of the Aβ deposits in the brains of AD patients. Applicant adds that zinc- and copper-specific chelators dramatically redissolve a significant proportion of Aβ extracted from post-mortem AD affected brain tissue. Finally, Applicant argues that the intramuscular administration of desferrioxamine, a chelator of copper and zinc, resulted in slowing the progression of AD (Crapper-McLachlan et al. Lancet 337:1304-1308, 1991). Applicant concludes that the *in vitro* results obtained with bathocuprione in the specification are indicative of the results that would be achieved when the chelator is administered to a subject.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the *in vitro* results obtained with bathocuprione may not necessarily be indicative of the results obtained with this metal chelator *in vivo*. For example, the extraction of Aβ from the cortex of AD brains was significantly enhanced in a dose dependent manner by the presence of the metal ion chelator, TPEN (Fonte et al., J Alzheimer's Disease 3: 209-219, 2001; see abstract; pg 210, ¶ 2). However, TPEN is of limited benefit to patients because it is highly toxic (Fonte et al., pg 217, ¶ 1). Additionally, a previous clinical trial of the chelator, desferrioxamine (DFO) was reported to significantly arrest the progression of AD (Cuajungco et al., Annals NY Acad Sci 920: 292-304, 2000; see pg 299, ¶ 4). However, DFO is a charged molecule that does not easily penetrate the blood-brain barrier and is easily degraded after administration (Cuajungco et al., pg 299 ¶ 4). Cuajungco et al. also disclose that the administration of DFO is associated with discouraging difficulties including the nonspecific problems of systemic metal ion depletion and the problem of administration of a twice-daily , painful intramuscular injection (pg 299, ¶ 4).

Additionally, there are several important points that must be taken into consideration before and during the administration of a metal chelator to a subject, which the instant specification has not addressed with bathocuprione. For example, Gnjec et al. (Frontiers Biosci 7 : 1016-1023, 2002) teach that if the levels of certain metals are decreased excessively below recommended levels, severe physiological side effects may result (under Part IV, important considerations in chelator therapy). Gnjec et al. also indicate that the depletion of metals should be localized to the site of pathology without a systemic depletion of metal ion concentrations. Gnjec et al. discuss that a prerequisite for successful treatment with any chelator will be the requirement for low toxicity and minimum side effects of the drug itself. Gnjec also add that a successful treatment strategy may involve a combination of several approaches for both the solubilization and inhibition of redox properties of Aβ in AD brain tissue (last ¶ under part IV).

The specification does not teach the administration of bathocuprione and indomethacin to a subject. Therefore, according to the references above, the positive *in vitro* results of using bathocuprione to extract Aβ from Aβ brain homogenates is not necessarily indicative of the results that may be obtained if bathocuprione is administered to subjects.

(iii) Applicant indicates that there are similar circumstances involving the chelator clioquinol to support of the assertion that results obtained in the *in vitro* system described in the specification accurately reflect the results that would be obtained in a subject. Applicant states that clioquinol, like bathocuprione, is a metal chelator that promotes the solubilization of Aβ *in vitro* (Cherny et al. Neuron 30: 665-676, 2001). Applicant argues that based on the *in vitro* results with this chelator, clioquinol was subsequently administered to a transgenic mouse model

of AD and was found to effectively inhibit brain Aβ deposition. Applicant also asserts that clioquinol was shown to improve cognitive parameters and blood levels of Aβ when administered to humans in a clinical trial. Applicant contends that the results with clioquinol indicate that a similar progression in the context of bathocuprione could have likewise been achieved using only routine experimentation. Applicant asserts that the evidence presented for clioquinol demonstrates that the process of determining dosage amount, duration of treatment, and route of administration for a chelator, in the context of treating amyloidosis, can be determined using only routine experimentation.

Applicant's arguments have been fully considered but are not found to be persuasive. Although clioquinol and bathocuprione may both be metal chelators, the positive *in vivo* results of the administration of clioquinol to a subject are not indicative of the results that might occur after the administration of bathocuprione. Clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) is specific for copper and zinc ions and has a different chemical make-up and structure than that of bathocuprione (2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline), which is specific for copper. Bathocuprione may have different physiological effects after administration to a subject than does clioquinol. Furthermore, one skilled in the art cannot predict that all metal chelators will have the same results after administration to a subject. For example, as discussed in part (ii) above, the metal chelators TPEN and DFO, have numerous problems after administration to a subject, such as toxicity and difficulty in crossing the blood-brain barrier. Undue experimentation would still be required of the skilled artisan to determine the proper dosage, duration, and route of administration of bathocuprione because bathocuprione is not

chemically/structurally related to clioquinol. Bathocuprione is a different compound which may have different effects in an individual.

(iv) Applicant argues that the passage cited by the Examiner from Gillmore merely indicates that, at the time of this reference, research in the area of amyloid deposit mobilization was ongoing. Applicant contends that the fact that others in the art had not been able to accomplish the results provided in the invention cannot form the basis for a proper enablement rejection. Applicant also states that there is no discussion whatsoever in Gillmore relating to the use of metal chelators in treating amyloidosis. Applicant submits that Gillmore provides no basis for assessing the predictability of the effects of a chelator on a subject. Applicant asserts that there is nothing in Gillmore to suggest that the effects of bathocuprione or bathocuprione/indomethacin in a subject would have been regarded as unpredictable.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, Gillmore et al. was cited by the Examiner to indicate the state of the art at the time the instant invention was made. For example, amyloid deposition is associated with a diverse range of disorders that includes Alzheimer's disease and the search continues for a treatment that causes the mobilization of amyloid deposits (abstract, pg 249, col 2). It is also noted that a broad, reasonable interpretation of the claims encompasses treatment of such diseases as Alzheimer's disease, which has proven to be recalcitrant to treatment in the art (see for example, Halliday et al., Clin Exp Pharmacol Physiol 27: 1-8, 2000). Although Gillmore et al. does not specifically discuss metal chelators, the art was such that amyloidosis was resistant to treatment.

Again, the acknowledgement of the state of the art at the time the invention was made is only one aspect of the Wands factors.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to determine the quantity of bathocuproine or bathocuproine/indomethacin to be administered, the most effective administration route, and the duration of the treatment, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of the composition *in vivo* (see Fonte et al., Cuajungco et al., Gnjec et al., Gillmore et al.), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, second paragraph

9. Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 1-2 recite the limitation "said chelator" in line 6 of claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

11. Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sigma Chemical Company (1995; catalog number B 1000; pg 149) in view of Goodman and Gilman (The Pharmacological Basis of Therapeutics, New York: McGraw-Hill, Inc, 1993; pg 5-6). The basis for this rejection is set forth at pg 7-8 of the previous Office Action (Paper No. 21, 26 August 2002).

Applicant's arguments (Paper No. 23, 26 February 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that Sigma simply lists bathocuprione as one of many chemical compounds and does not provide any indication or suggestion that bathocuprione can be included in a pharmaceutical composition or that it can be combined with a pharmaceutically acceptable carrier or diluent. Applicant argues that Goodman provides only a general statement regarding factors that influence the absorption of drugs. Applicant contends that there is nothing in the cited passage from Goodman that suggests combining a pharmaceutically acceptable carrier or diluent with bathocuprione or any other metal chelator. Applicant submits that neither Sigma nor Goodman provide any specific suggestions or motivation to combine bathocuprione with one or more pharmaceutically acceptable carriers or diluents. Applicant states that simply because drugs in general are more rapidly absorbed in a subject when put into an aqueous solution does not in any way suggest the specific combination of metal chelator with an aqueous solution. Applicant notes that the mere fact that an advantage might be realized by combining reference teachings does not mean that a skilled artisan would be motivated to make the combination. Applicant adds that there has been nothing specifically cited that indicates the need or desirability of improving the absorption of metal chelators in a subject.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, in response to applicant's arguments, the recitation "a pharmaceutical composition for treatment of conditions caused by amyloidosis" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and

where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). Therefore, claim 37 reads on bathocuprione or a hydrophobic derivative thereof and a pharmaceutically acceptable carrier or diluent.

Sigma teaches a crystalline form of the metal chelator, bathocuprione, while Goodman et al. teach that that drugs can be in several forms, such as in an oily suspension, solid form, suspension, or in water. One skilled in the art would not have been able to utilize Sigma's bathocuprione in the form that it comes in (crystalline) and would have added it to water or other liquid solution, as taught by Goodman et al. Claim 37 of the instant application reads on such a composition.

Conclusion

Claim 53 is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
May 12, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER